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Ecofriendly Synthesis of Antifungal Azoles

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요 약. 1,2,4-트라이아졸, 피라졸론, 그리고 1,3,4-옥사다이아졸을 마이크로파 쬐임(MWI) 하에서 여러 가지 고체지지체를 이용하여 치환기가 있는 하이드라자이드로부터 합성하였다. 그 얻어진 실험 결과들은 고체지지체의 다양성을 보여준다. 합성한 모든 유도체들을 *A. niger*와 *A. flavus* 균주에서 항진균성활성도를 조사한 하였으며 좋은 활성을 보여주었다.

주제어: 고체지지체, 마이크로파 쬐임, 항진균성 활성도, 트라이아졸, 피라졸론, 옥사다이아졸

ABSTRACT. 1,2,4-Triazoles, pyrazolones and 1,3,4-oxadiazoles have been synthesized from substituted hydrazide using various solid supports under microwave irradiation (MWI). The results obtained highlight the versatility of the solid supports. All synthesized compounds were screened for their antifungal activity against *A. niger* and *A. flavus* and were found to possess good activity.

Keywords: Solid Support, Microwave Irradiation (MWI), Antifungal Activity, Triazoles, Pyrazolones, Oxadiazoles

INTRODUCTION

The increasing environmental consciousness throughout the world has put a pressing need to develop an alternate synthetic approach for biologically and synthetically important compounds. Inorganic solid supports (aluminas, silicas, zeolites, clays) coupled with microwaves have made a landmark in this direction as reactions can be performed in dry media or under solventless conditions.[1,2] Aluminas can be selected as acidic or basic catalyst depending on the type of organic reaction. Montmorillonite clays such as K10 offer acidities very close to nitric acid or sulfuric acid.[3] Moreover, these mineral oxides act as an efficient energy transfer medium.

1,2,4-Triazoles, pyrazolones and 1,3,4-oxadiazoles are associated with broad spectrum of biological activities including antifungal, antibacterial, anti-inflammatory, antihistaminic, analgesic and antitumor properties.[4-9] Several methods for the synthesis of these biologically active compounds are reported in literature.[10,11] Hydrazide derivatives have been extensively used as a good precursor for the synthesis of these derivatives.[12,13] Keeping in view the biological importance of the above mentioned heterocyclic compounds and in continuation to our endeavour towards environmentally benign synthesis,[14] we report herein the synthesis of 3-[(2-benzoylamino)phenyl]-1,2,4-triazolin-5-thione **2a,b**, 3-methyl-1-[(2-benzoylamino))benzoyl]-5-pyrazolone **3a,b** and 2-[(2-benzoylamino) phenyl]-5-aryl-1,3,4-oxadiazoles **4a,b** from 2-(benzoylamino) benzoic hydrazide **1a** and 2-benzoylaminobenzoic phenylhydrazide **1b** using different solid supports under

MWI. These derivatives were screened for their antifungal activity against *A. niger* and *A. flavus*.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. ^{1}H NMR were recorded on FT NMR Hitachi R-600 (60 MHz) instrument using tetramethyl silane as reference. Microwave irradiation was carried in Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W). Elemental analysis were performed by means of Heraeus CHN-Rapid Analyzer. The progress of reaction was monitored on silica gel coated Al plates (Merck). Temperature of the reaction mixture was measured through AZ. Non-Contact IR thermometer, Model No. 8868.

General Procedure for the synthesis of 3-[(2-benzoylamino)phenyl]-1,2,4-triazolin-5-thione (2a,b)

Compound **1a,b** was prepared according to the literature method.[15,16]

Table 1. Antifungal Activity of Compounds (**2a, b; 3a, b; 4a, b**)

Compd. No.	Inhibition of *A. niger* (50 μg/mL)	Inhibition of *A. flavus* (50 μg/ML)
2a	−++	−−+
2b	−++	−+−+
3a	−+−+	−++−+
3b	−+−+	−++−+
4a	·	·
4b	·	·
Salicyclic acid	·	·

+ − 3-9 mm; +− − 10-12 mm; −++ − 13-16 mm; −−−− − 17-21 mm; −−−−+ − >21 mm.

Basic alumina/neutral alumina[18] (20 g) was added to a solution of **1a,b** (0.01 mol) and ammonium thiocyanate (0.01 mol) in ethanol (20 mL) at room temperature. The reaction mixture was thoroughly mixed and air dried (in 100 mL beaker). It was then placed in an alumina bath inside the microwave oven and irradiated intermittently at 30s intervals for the specified time (*Table* 2). On completion of reaction, as monitored by TLC examination (at an interval of 30s), the product was extracted into chloroform (3×10 mL). Removal of solvent under reduced pressure gave the desired product (*Table* 2) which was recrystallized from ethanol.

General Procedure for the synthesis of 1-[(2-benzoylamino)benzoyl]-3-methyl-5-pyrazolone (3a,b)

To the ethanolic (20 ml) solution of **1a,b** (0.01 mol) and ethyl acetoacetate (0.01 mol) in 100 ml beaker, neutral alumina (20 g) was added. The reaction mixture was stirred well and dried in air. It was placed in an alumina bath and subjected to MWI intermittently at an interval of 30s for specified time (*Table* 2). On completion of reaction, as monitored by TLC examination (at an interval of 30s), the product was extracted into ethanol (3×10 mL). Removal of solvent under reduced pressure gave the desired product (*Table* 2) which was recrystallized from ethanol.

General Procedure for the synthesis of 5-[2-(benzoylamino)phenyl]-2-aryl-1,3,4-Oxadiazole (4a,b)

To the ethanolic solution of **1a** (0.01 mol) and carboxylic acid **5a,b** (0.01 mol) in 100 ml beaker, acidic alumina montmorillonite K10 clay (20 g) was added. The reaction mixture was stirred well and dried in air. It was then placed in an alumina bath and subjected to MWI intermittently at an

Table 2. Comparison of Reaction Time & Yield for Compounds (**2a, b; 3a, b; 4a, b**)

Compd. No.	m.p. (°C)	Conventional Heating Solution Phase		Microwave Heating Solid Support	
		Time (hr)	% Yield	Time (min)	% Yield
2a	175	3.0	77	2.5[a] (2.0)[b]	92[a] (91)[b]
2b	188	3.5	76	3.5[a] (2.5)[b]	90[a] (91)[b]
3a	192	4.5	74	5.0	87
3b	180	6.0	75	6.0	88
4a	168	4.0	77	7.0[c] (7.5)[d]	89[c] (87)[d]
4b	179	5.5	72	6.5[c] (7.5)[d]	90[c] (86)[d]

[a]Neutral alumina; [b]Basic alumina; [c]Acidic alumina; [d]Montmorillonite K10 clay.

interval of 30s for specified time (*Table* 2). On completion of reaction, as monitored by TLC examination, the product was extracted into ethanol (3×15 mL). Removal of solvent under reduced pressure gave the desired product (*Table* 2) which was recrystallized from ethanol.

RESULTS AND DISCUSSION

The hydrazides **1a,b** were prepared by treating 2-phenyl-3,1-benzoxazin-4-one with hydrazine hydrate and phenylhydrazine respectively.[15,16] Condensation of **1a,b** with ammonium thiocyanate was carried over basic/neutral alumina under MWI to give 3-substituted-1,2,4-triazolin-5-thione **2a,b**. This was evidenced by appearance of IR absorption band at 1240 cm^{-1} (C=S) and 1580 cm^{-1} (C=N) and appearance of signal for NH at δ 8.3 in ^{1}H NMR spectrum. Time taken for the completion of reaction using basic alumina was less than that with neutral alumina though the yields were comparable (*Table* 2). This is because in basic media the increase in nucleophilicity of nitrogen leads to attack at carbonyl carbon through nitrogen.

Condensation of **1a,b** with ethyl acetoacetate using neutral alumina afforded the 3-methyl-1-substituted-5-pyrazolone **3a,b**. The formation of the compounds was evidenced by the disappearance of IR band at 1720 cm^{-1} due to C=O of ester and appearance of band at 1660 cm^{-1} due to C=O of pyrazolone ring. In ^{1}H NMR signal at δ 5.5 due to H-4 proton and at δ 2.3 due to methyl protons were present.

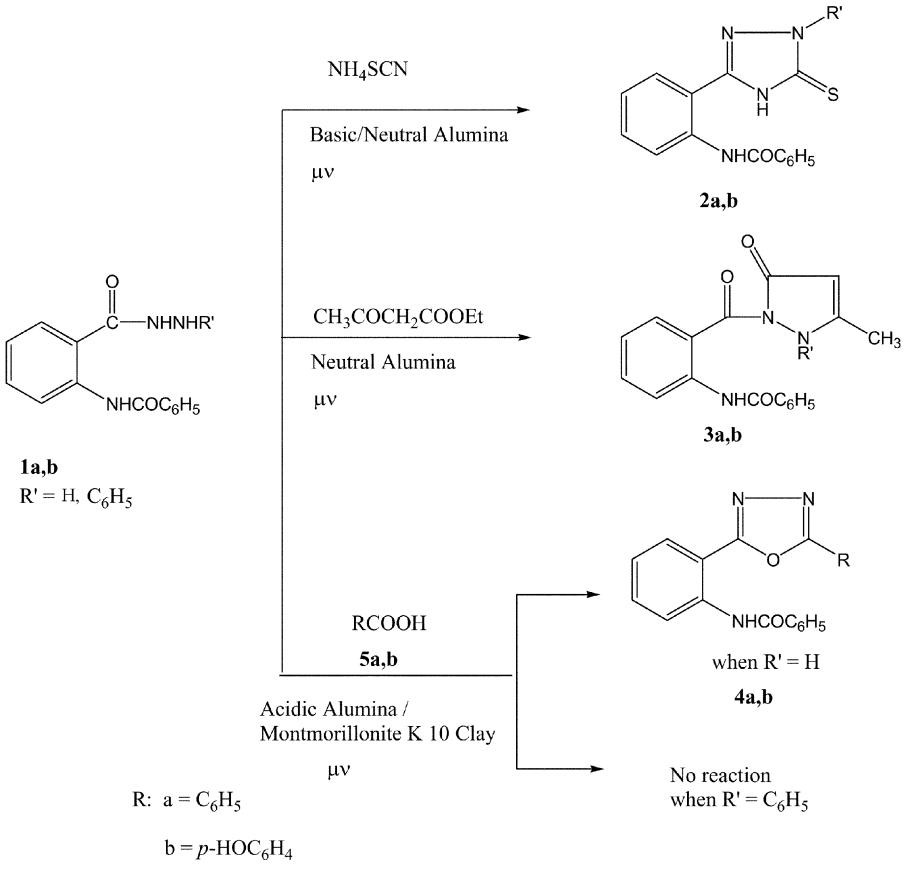
In continuation of our earlier effort for novel route towards synthesis of 2,5-disubstituted-1,3,4-oxadiazole[17], **1a,b** when condensed with aromatic carboxylic acids **5a,b** under MWI using acidic alumina/montmorillonite K10 clay[18] gave new 1,3,4-oxadiazoles in good yield in case of **1a** only, while no product was obtained with **1b** even after irradiating for long time. Moreover, the formation of intermediate diacylhydrazide was not observed in this case. This is due to the decrease in the nucleophilicity of nitrogen in acidic media and also the presence of electron withdrawing phenyl group. The structure of the compound was established by the appearance of IR band at 1590 cm^{-1} (C=N) and disappearance of band at 1725 cm^{-1} (C=O) of carboxylic acid. The band at 1337 cm^{-1} (C-O-C) characteristic of cyclic ether further confirmed the formation of products.

Elemental analysis of all compounds was done (*Table* 3). The compounds **2a,b, 3a,b** and **4a,b** were also synthesized under conventional heating. The drastic reduction in reaction time and improvement in yield on going from conventional synthesis to microwave assisted solid support synthesis (*Table* 2) can be attributed to the uniform heating effect of microwaves. Reaction pathways are depicted in *Scheme* 1.

All compounds were screened for their antifungal activity against *A. niger* and *A. flavus* by the paper disc diffusion method.[18] The zone of inhibi-

Table 3. Spectral and Analytical Data of the Compounds (2a, 2b, 3a, 3b, 4a, 4b)

Compd. No.	IR (ν, KBr pellets) cm^{-1}	^{1}H NMR (δ, ppm $CDCl_3$)	% CHN. Found (Calcd.)		
			C	H	N
2a	3420, 3210 (N-H), 1670 (C=O),	7.2-7.7 (m, 9H, Ar-H);	60.78	4.07	18.90
	1240 (C=S), 1580 (C=N)	8.3 (br, 2H, 2 x NH)	(60.81)	(4.05)	(18.91)
2b	3218 (N-H), 1678 (C=O),	7.2-7.8 (m, 14H, Ar-H),	67.75	4.33	15.07
	1580 (C=N), 1245 (C=S)	8.4 (br, 1H, NH)	(67.74)	(4.30)	(15.05)
3a	3420, 3280 (N-H),	2.3 (s, 3H, CH_3), 5.5 (s, 1H, CH),	67.30	4.68	13.10
	1700, 1685, 1680 (C=O)	7.3-8.0 (m, 9H, ArH), 8.4 (br, 1H, NH)	(67.28)	(4.67)	(13.08)
3b	3440 (NH), 1695, 1685,	2.4 (s, 3H, CH_3), 5.4 (s, 1H, CH),	72.56	4.75	10.58
	1680 (C=O)	7.3-8.0 (m, 14H, Ar-H)	(72.54)	(4.78)	(10.57)
4a	1590 (C=N),	7.2-8.3 (m, 14H, Ar-H),	73.91	4.35	12.29
	1339 (COC)	10.8 (br, 1H, NH)	(73.90)	(4.39)	(12.31)
4b	1564 (C=N), 1337 (COC),	5.5 (s, 1H, OH), 7.0-7.8 (m, 13H, Ar-H),	70.60	4.22	11.75
	3308 (OH)	10.7 (br, 1H, NH)	(70.58)	(4.20)	(11.76)



Scheme 1.

tion was measured in millimeters. The antifungal activities of the test compounds were compared to standard salicylic acid (17-21 mm). DMF was used as solvent. All compounds have shown good activity against both fungi. However, pyrazolone derivatives **3a,b** have shown excellent antifungal activity (20-22 mm) against both *A. niger* and *A. flavus*. Compound **4a,b** showed better activity (15-17 mm) against *A. niger* as compared to activity (11-13 mm) against *A. flavus* (*Table* 1).

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18. (a) Aluminium oxide, acidic, Brockmann I (~ 150 mesh, 58 Å, CAMAG 506-C-1, surface area 155 m^2/g). (b) Montmorillonite K10 clay, Aldrich 11,6168, surface area 220-270 m^2/g, Bulk density 300-370 g/l. (c) Aluminium oxide neutral, Brockmann I (Aldrich Chem. Co., Cat. No. 19, 997-4, ~ 150 mesh, 58 Å, surface area 155 m^2/g). (d) Aluminium oxide basic, Brockmann I (Aldrich Chem. Cat. No. 19, 944-3, ~ 150 mesh, 58 Å, surface area 155 m^2/g).